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REVIEW ARTICLE

Lapatinib in the treatment of HER-2 overexpressing breast cancer

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Summary

Lapatinib is the only clinically available agent for the treatment of patients with human epidermal growth factor receptor-2 (HER-2) positive tumors that have progressed on treatment with trastuzumab, taxanes and anthracyclines. Moreover, when given with letrozole in postmenopausal patients with estrogen receptor (ER) and HER-2 positive disease it induces clinically meaningful benefit. Recently presented neoadjuvant data suggests an important place for the combination of trastuzumab and lapatinib in the therapy of early HER-2 positive breast cancer. This article reviews the current status and future perspectives of lapatinib.

Key words: breast cancer, HER-2, lapatinib, targeted therapy

Introduction

Breast cancer is the most common malignancy in females, and the leading cause of cancer-related mortality among women worldwide [1,2]. Many advances in screening, early diagnosis and adjuvant treatment led to significant improvement in prognosis of early-stage disease [3]. But, despite all those adjuvant treatments, approximately one third of patients develops metastasis. Although today many therapeutic options are available which prolong survival and improve the quality of life for these patients, metastatic disease is still an incurable condition and remains a challenging clinical problem [3]. Understanding of breast cancer as a biologically heterogeneous disease and the molecular pathways of breast cancer development and progression, have led to development of new generation of the, so-called, biologic targeted drugs [4]. Potential targets are signaling pathways recruited by the tumor for progression and survival. The ErbB receptor family has a pivotal role in breast cancer [4]. It is a family of tyrosine kinase (TK) receptors including 4 homologous members: ErbB1, also known as epidermal growth factor receptor (EGFR); ErbB2, also known as HER-2; ErbB3; and ErbB4. At diagnosis approximately one quarter of patients have overexpressed HER-2 receptor [3]. Patients with HER-2 positive tumors have more aggressive disease, increased propensity of disease relapse and death from breast cancer [1,3]. Following the facts stated above, the next logical step was to develop receptor-targeted treatments for HER-2 positive breast cancer. Current agents evaluated in clinical trials are monoclonal antibodies (trastuzumab, pertuzumab), antibody-drug conjugates (trastuzumab DM1), TK inhibitors (lapatinib), and heat-shock protein 90 inhibitors [1,5-7]. Monoclonal antibodies bind to the extracellular domain of the receptor, recruiting cytotoxic lymphocytes and perturbing HER-2 mediated signaling pathways to result in cell cycle arrest in G_1 [5]. The first clinically used monoclonal antibody was trastuzumab and now it represents a cornerstone treatment for HER-2 positive breast cancer, demonstrating survival benefits in both adjuvant and metastatic setting [3,5,8]. Trastuzumab binds with high specificity and affinity to the extracellular domain IV of the HER-2 [5]. The way of inhibiting HER-2 receptor is not fully understood and possible mechanisms of action are as follows: inhibition of pathways involved in cell cycle progression, proteolytic cleavage of the HER-2 receptor, inhibition of tumor angiogenesis and of DNA damage repair pathways, as well as of antibody-dependent cellular cytotoxicity [3,5,9]. Although trastuzumab nowadays represents the gold standard of care for HER-2 positive disease, there are still many unresolved problems in its clinical efficacy, such as drug resistance (*de novo* and acquired), cardio-

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toxicity and lack of penetration through the blood-brain barrier [10]. Due to the lack of penetration of blood-brain barrier, trastuzumab is associated with an increased risk of central nervous system (CNS) metastasis as a site of the first tumor recurrence [5,10]. Also, most patients with metastatic disease tend to progress within one year from the beginning of treatment with trastuzumab [11-14]. Therefore, there is a need for development of new therapeutic options in the treatment of HER-2 positive disease that are more efficacious, better tolerated and may overcome trastuzumab resistance. Lapatinib, a dual TK inhibitor (EGFR and HER-2) is registered for the clinical use in HER-2 positive metastatic breast cancer (MBC) treatment in combination with either chemotherapy or hormonal therapy. Our review deals with the current clinical use of lapatinib and examines potential future directions of its use.

Lapatinib

Lapatinib is an orally available, small-molecule, reversible inhibitor of both EGFR and HER-2. Recent data have shown that EGFR specific inhibitors can reduce HER-2 signaling and consequently the growth of HER-2 positive breast cancer cells. Thus, the combined inhibition of both EGFR and HER-2 may be more effective than targeting separate receptors [15]. Lapatinib works intracellularly, directly targeting the TK domain. This small molecule reversibly binds to the cytoplasmic ATP-binding site of the kinase and blocks the receptor phosphorylation and activation. This interaction prevents the phosphorylation and the subsequent signal transduction of Ras/Raf mitogen-activated protein kinases (MAPKs) and PI3K (phosphatidylinositol-3-kinase)/Akt pathways, leading to an increase in apoptosis and decreased cellular proliferation [16]. In preclinical studies, lapatinib was not cross-resistant with trastuzumab [17,18]. There are some potential advantages of lapatinib in comparison with trastuzumab. Lapatinib inhibits both EGFR and HER-2, while trastuzumab targets only the extracellular domain of HER-2. Inhibition of only one receptor may not be effective in inhibiting heterodimers containing both HER-1 and HER-2. Also, the intracellular activity of lapatinib may be advantageous in the treatment of tumors expressing truncated forms of both HER-1 and HER-2 lacking their extracellular domain, because antibodies targeting the external domains of these proteins do not recognize these truncated forms [19].

The recommended dosage of lapatinib in combination with capecitabine (2000 mg/m^2, days 1-14 in 21-day cycles) is 1250 mg/day (5 tablets of 250 mg) continuously. In case of lapatinib administration with letrozole, the dose of lapatinib is 1500 mg daily. Lapatinib should be taken at least 1 hour before of after a meal. Since lapatinib is an inhibitor of CYP3A4, if concomitant medication with some other CYP3A4 inhibitor is given, a dose reduction of lapatinib should be considered in order to prevent toxicity [20]. The effective plasma half-life is approximately 24 hours [21].

Lapatinib in metastatic breast cancer

Clinical trials explored lapatinib in monotherapy and concomitantly with chemotherapy and hormonal therapy, mainly in heavily pretreated patients with MBC. Early trials (phase I and II) revealed good tolerance and preliminary single-agent clinical activity for lapatinib monotherapy, despite multiple lines of prior chemotherapy and trastuzumab, indicating that lapatinib is active beyond progression after standard treatments [22-25].

Lapatinib in combination with chemotherapy in metastatic breast cancer

Lapatinib was introduced in clinical practice for MBC treatment in combination with capecitabine. Approval of lapatinib in clinical practice was based on the results of EGF100151 trial. This was a randomized, open-label, phase III trial which enrolled 324 women with HER-2 positive, locally advanced breast cancer or MBC progressed after treatment with regimens containing an anthracycline, a taxane, and trastuzumab [26]. Patients were randomly assigned to receive either lapatinib (1250 mg daily, continuously) in combination with capecitabine (2000 mg/m^2 per day in two divided doses for 14 consecutive days, with 1 week rest) or capecitabine alone (2500 mg/m^2 per day in two divided doses for 14 consecutive days, with 1 week rest), until tumor progression or unacceptable toxicity. The primary endpoint was time to progression (TTP). The first interim analysis showed that the addition of lapatinib to capecitabine was associated with a 51% reduction in the risk of disease progression (hazard ratio, [HR] 0.49, $p<0.001$) with median TTP of 8.4 months in the combination arm vs. 4.4 months in the monotherapy arm). Median progression free survival (PFS) was 8.4 vs. 4.1 months (HR 0.47, $p<0.001$). The overall response rate (ORR) was 23% in the combination arm and 14% in the monotherapy arm ($p=0.113$). Based on the above efficacy results, the primary endpoint (TTP) met the pre-specified criteria, and the Data and Safety Monitoring Committee decided to close the study at that first interim analysis when 321 of 324 patients

were enrolled. The most common adverse events (AEs) included diarrhea (58 vs. 39%), hand-foot syndrome (43 vs. 34%), and rash and/or skin reaction (35 vs. 30%) (all grades, for the combination arm vs. capecitabine alone). In conclusion, the improvement in efficacy was obtained without increase in serious toxicity.

Recent updates of the results of this trial have confirmed the previously reported data. In fact, the combination of lapatinib and capecitabine prolonged the TTP (HR 0.57, p<0.001) and provided a trend toward improved overall survival (OS), with an HR of 0.78 (p= 0.177). Also, interestingly, an exploratory analysis showed that the incidence of CNS metastases as the first site of progression was lower for patients treated with the combination of lapatinib and capecitabine. Only 4 (2%) patients receiving the combination vs. 13 (6%) receiving capecitabine monotherapy experienced CNS metastases (p=0.045) [27].

The combination of lapatinib and paclitaxel in HER2-negative or unknown MBC patients, as first line treatment, was tested on 579 women in a phase III EGF30001 trial [28]. Patients were randomly assigned to receive either paclitaxel (175 mg/m^2, every 3 weeks) plus lapatinib (1500 mg daily) or paclitaxel (175 mg/m^2, every 3 weeks) with placebo. The primary endpoint was TTP. In the intention to treat (ITT) analysis, there were no statistically significant differences in TTP, event-free survival (EFS) and OS between the treatment arms. An advantage in ORR (35.1 vs. 25.3%, p=0.008) and clinical benefit rate (CBR) (40.5 vs. 31.9%, p=0.025) was observed [28].

A preplanned retrospective analysis of HER-2 status was performed using immunohistochemistry and fluorescence *in situ* hybridization. Out of 579 patients randomized, 86 (15% of the enrolled patients) were found to be HER-2 positive. A subset analysis performed on these HER-2 positive patients showed a statistically significant superiority of the combination of lapatinib and paclitaxel in TTP (36.4 vs. 25.1 weeks, HR 0.53, p=0.005), EFS (35.1 vs. 21.9 weeks, HR 0.52, p=0.004), ORR (63.3 vs. 37.8%, p=0.023) and CBR (69.4 vs. 40.5%, p=0.011). Median OS was longer in the paclitaxel-lapatinib arm compared to the paclitaxel-placebo arm (104.6 vs. 82.4 weeks), however this difference was not statistically significant (p=0.365) [28].

The addition of lapatinib to paclitaxel resulted in increased grade 3 rash (4 vs. 0% for placebo) and grade 3 diarrhea (15 vs. 1% for placebo). No differences in cardiac events were seen between treatment arms [28]. In conclusion, this trial did not confirm any activity of lapatinib in combination with paclitaxel as a first line treatment for HER-2 negative MBC patients. In contrast, a preplanned, blind evaluation showed that the combination of lapatinib and paclitaxel is clinically significantly better than monochemotherapy with paclitaxel in terms of ORR, CBR, TTP and EFS.

Lapatinib in combination with endocrine therapy in metastatic breast cancer

Cross-talk between pathways involving the ErbB receptor family, especially EGFR and HER-2, and the ER has been implicated in resistance to endocrine therapy [29]. That was the rationale for the trials using combination of lapatinib and hormonal therapy. Preclinical trials have shown promising results when combining endocrine therapy and HER-1/HER-2 inhibitors [30]. Lapatinib seems to be able to overcome hormonal resistance due to inactivation of ErbB -family signaling, either in HER-2 positive or negative breast cancer [30]. A phase I combination study with lapatinib and letrozole showed potential clinical benefit [31]. Based on those promising results, a phase III trial (EGF30008) of letrozole/lapatinib vs. letrozole/placebo was initiated. The study included 1286 postmenopausal women with hormone receptor (HR) positive MBC who had not received any prior treatment for metastatic disease [32]. In the 219 patients with HR positive and HER-2 positive MBC, the addition of lapatinib to letrozole significantly increased the median PFS (8.2 months), with 29% benefit over the 3 months median PFS seen with letrozole alone (HR 0.71; p=0.019). Furthermore, the CBR with the combination was 48%, compared with 29% with letrozole monotherapy (p=0.003), while the ORR was significantly improved from 15% to 28% for patients treated with letrozole plus lapatinib (p=0.021). Grade 3 or 4 AEs were more common in the combination arm (diarrhea 10 vs. 1%; rash 1 vs. 0%). In patients (n=952) with HR-positive/HER-2 negative MBC no PFS improvement was observed (median PFS 13.4 vs. 13.7 months; p=0.188). A recently performed quantitative ER and progesterone receptor (PgR) analysis in 821/952 HER-2 negative tumors demonstrated that patients with the lowest quartile of ER expression obtained a significant improvement in median PFS from the association of lapatinib with letrozole (13.6 vs. 6.6 months; p<0.005), compared to those with higher level of ER expression [33]. The efficacy of lapatinib in HER-2 negative and ER positive tumors also varied by the degree of PgR expression; benefit was only seen in PgR-weak patients while PgR-strong patients derived no benefit and PgR-negative appeared to have worse outcome on lapatinib [33]. These findings are based on very small subgroups and also lack strong biological rationale, so further investigation on larger population is required. Lapatinib/letrozole combination

brings a good quality of life, showing greater quality-adjusted survival as compared to letrozole alone [34]. Cardiac safety of this combination revealed a low rate of incidence of cardiac AEs, with similar occurrence irrespective of previous anthracycline exposure in the adjuvant setting [35]. In conclusion, this phase III trial confirmed that lapatinib and letrozole combination is clinically meaningful, with good efficacy/toxicity ratio and should consecutively be used as a treatment option for ER and HER-2 positive postmenopausal MBC patients.

Lapatinib/trastuzumab combination in metastatic disease

Lapatinib was also investigated in metastatic disease in combination with the current gold standard for HER-2 positive breast cancer (trastuzumab) in heavily pretreated patients. This study was based on preclinical findings in HER-2 positive cells of a synergistic interaction between lapatinib and trastuzumab [17].

In the phase III EGF104900 trial patients with HER-2 positive MBC who experienced progression on prior trastuzumab-containing regimens were randomized to receive either lapatinib alone or combination of lapatinib and trastuzumab [36]. The primary endpoint of the study was PFS while secondary endpoints were ORR, CBR and OS. In the ITT (296 patients), the combination of lapatinib and trastuzumab was more efficacious than lapatinib alone for PFS (HR 0.73, p=0.008) and CBR (24.7 vs. 12.4%, p=0.01), with a trend towards improved OS (HR 0.75, p=0.106). No difference in ORR was observed (10.3% in the combination arm vs. 6.9% in the monotherapy arm, p=0.46). The most frequent AEs were diarrhea (statistically more frequent in the combination arm, p=0.03), rash, nausea and fatigue, while the incidence of cardiac events was very low and similar between the two arms [36]. The conclusion of the authors was that the combination of lapatinib and trastuzumab is a clinically valuable chemotherapy-free option with an acceptable safety profile for patients with HER-2 positive MBC progressing on trastuzumab-containing therapy.

Head-to-head comparison between lapatinib and trastuzumab in combination with a taxane (either docetaxel or paclitaxel) in the first-line treatment of HER-2 positive MBC is ongoing in the COMPLETE trial [37].

Neoadjuvant clinical trials of lapatinib

Results from two phase III studies examining the effect of lapatinib in the neoadjuvant setting of locally advanced, operable HER-2 positive breast cancer were recently presented. The combination of lapatinib and trastuzumab with standard chemotherapy was compared to standard chemotherapy plus either lapatinib or trastuzumab in a trial called NeoALTTO. In the GeparQuinto trial, lapatinib plus standard chemotherapy was compared to trastuzumab plus standard chemotherapy. The primary endpoint for the NeoALTTO and the GeparQuinto was pathological complete response (pCR) defined as the absence of invasive cancer cells in the breast at surgery. In the NeoALTTO, 450 HER-2 positive patients were randomized to one of three arms: to receive lapatinib plus paclitaxel or trastuzumab plus paclitaxel or a combination of lapatinib and trastuzumab plus paclitaxel. Results from the 18 weeks of therapy prior to surgery showed the pCR rate was 51.3% in the lapatinib plus trastuzumab combination arm compared to a rate of 24.7% for the lapatinib arm and 29.5% for the trastuzumab arm [38]. The difference in pCR between the lapatinib plus trastuzumab arm compared to the lapatinib and trastuzumab arms was statistically significant (p=0.0001). The pCR difference between the lapatinib and trastuzumab arms was not statistically significant (p=0.34) [38]. Looking at pCR by HR status, the observed benefit of the combination of lapatinib and trastuzumab was more robust in HR negative patients than in HR positive patients (61.3 vs. 41.6%). Grade 3 AEs encountered for lapatinib, trastuzumab and lapatinib/trastuzumab combination respectively were: diarrhea (23, 2 and 21%), neutropenia (16, 3 and 9%), hepatic (13, 1 and 9%), and skin disorders (7, 3, and 7%). No major cardiac dysfunction occurred. The study is continuing for secondary endpoints (OS, DFS and safety) [38]. In the NeoALTTO, a higher level of pCR was obtained by the dual inhibition of the HER-2 pathway using an antibody, trastuzumab, and a small molecule, lapatinib, compared with either agent alone. It is an important and interesting scientific result which emphasizes the potential importance of dual approach in the process of HER-2 blockade.

GeparQuinto planned to include more than 2500 patients, both HER-2 positive and HER-2 negative. The HER-2 positive cohort included 620 HER-2 positive breast cancer patients and compared lapatinib vs. trastuzumab given concomitantly with anthracycline-taxane-based therapy. Both groups received trastuzumab post surgery. The study results show that both the lapatinib and trastuzumab therapies demonstrated an ability to reduce the presence of tumor residuals in the breast and nodes at the time of surgery [39]. The pCR (no invasive or noninvasive residual disease in the breast and nodes) was 31.1% in the chemotherapy plus trastuzumab arm and 21.7% in the chemotherapy plus lapatinib arm (p <

0.05). Using no invasive residual disease in the breast and lymph nodes as criteria, the trastuzumab arm obtained a pCR of 45% while the lapatinib arm achieved a pCR of 29.9% ($p < 0.05$). Using no invasive residual disease in the breast as criterion, pCR was 50.4% for trastuzumab and 35.2% for lapatinib ($p < 0.05$). At surgery, the breast-conservation rate was 65.6% for the trastuzumab arm and 56% for the lapatinib arm [39]. The rate of discontinuation was higher in the lapatinib arm than in the trastuzumab arm (23 vs. 13%) due to side effects, mainly diarrhea [39]. The study is ongoing for secondary endpoints, which include OS, DFS and safety.

Lapatinib in the adjuvant setting

One of the most challenging fields of the evaluation of the efficacy of lapatinib is represented by its use in the adjuvant setting of HER-2 positive breast cancer. Two adjuvant trials with lapatinib are initiated; the TEACH and the ALTTO.

A phase III randomized, double-blind, multicenter, placebo-controlled study of delayed adjuvant lapatinib, the TEACH trial, is designed to compare the efficacy and safety of lapatinib vs. placebo in patients with HER-2 positive early-stage breast cancer who had already received primary adjuvant therapy (no adjuvant trastuzumab) and who have no clinical or radiological evidence of disease [40]. The aim of this trial is to determine whether adjuvant therapy with lapatinib for 1 year will improve DFS in women with early stage HER-2 overexpressing breast cancer.

The ALTTO trial is a randomized, open label, multi-centre phase III study comparing the activity of lapatinib alone vs. trastuzumab alone vs. trastuzumab followed by lapatinib vs. lapatinib concomitantly with trastuzumab in the adjuvant treatment of patients with HER-2 overexpressing and/or amplified breast cancer [41]. The primary objective of this study is to compare DFS in patients with HER-2 positive breast cancer randomized to trastuzumab for one year vs. lapatinib for one year vs. trastuzumab (12 or 18 weeks, according to assigned design) followed by a six-week treatment-free interval followed by lapatinib (28 or 34 weeks, according to assigned design) vs. trastuzumab in combination with lapatinib for one year (52 weeks). Secondary objectives include treatment comparisons with respect to OS, time to recurrence, time to distant recurrence, safety and tolerability, incidence of brain metastasis, and analyses conducted separately for cohorts of patients defined by the presence or absence of cMyc oncogene amplification, expression level of PTEN and presence or absence of the p95HER2 receptor [41].

Safety profile of lapatinib

In general, lapatinib is a well tolerated drug. The most common toxicities related to lapatinib monotherapy were diarrhea (54%), rash (30%), nausea (24%), vomiting (14%), fatigue (14%), and anorexia (10%) [42]. A recent meta-analysis of randomized phase III trials with lapatinib indicates a substantial increase in serious drug-related toxicities with lapatinib-based regimens compared to the same regimen without lapatinib. Overall, lapatinib-based treatment was associated with 64% increased odds of developing a serious adverse event (SAE) compared to the same treatment without lapatinib ($p = 0.003$) [43]. Patients receiving lapatinib were more likely to discontinue their therapy due to drug toxicity [43]. Although not statistically significant, this increase in toxicity appeared more pronounced when lapatinib was combined with endocrine therapy rather than chemotherapy, which is probably due to intrinsic lower toxicity of hormonal therapy in comparison with chemotherapy [32,43]. Lapatinib did not appear to significantly upgrade toxicities from chemotherapy [43]. The most frequent SAEs were diarrhea, rash, arthralgia and fatigue. Severe nail toxicity was infrequent and occurred in less than 1% of the patients. The excess in SAEs appeared specific to the known toxicity profile of lapatinib, with patients more likely to suffer from severe diarrhea and rash.

Conclusion

Lapatinib is the only TK inhibitor approved for use in HER-2 positive MBC in combination with capecitabine after trastuzumab, anthracycline and taxane treatment failures. It is also approved for ER and HER-2 positive MBC in postmenopausal patients in first line treatment in combination with letrozole. It is important to highlight that, for now, only HER-2 positive patients have clinical benefit from lapatinib, and consequently, treatment of HER-2 negative patient is not indicated. Future trials will have to answer on some, until now, unanswered questions such as ability of this small molecule to overcome hormonal and trastuzumab resistance, benefit in HER-2 negative tumors and its role in the neoadjuvant and adjuvant settings.

Disclosure statement

Professor Eduard Vrdoljak, MD PhD, was speaker on various occasions for GlaxoSmithKline and has consultant or advisory role. Marijo Boban, MD and Marija Ban, MD have nothing to disclose.

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